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BENZENE AND LYMPHOHEMATOPOIETIC MALIGNANCIES IN CHINA

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Benzene is a widespread contaminant in air and groundwater, deriving from industrial sources, cigarette smoke, gasoline, and automobile emissions (Wallace, 1989). There is scientific agreement that benzene causes leukemia, particularly acute nonlymphocytic leukemia (ANLL) and its subgroup of acute myeloid leukemia (AML), but controversy exists with regard to the level of risk at low exposures and the potential association with other lymphohematopoietic malignancies (Hricko, 1994; Savitz & Andrews, 1996). The epidemiologic basis for a dose-response relation-

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ship for leukemia has been based primarily on three small cohort studies (Rinsky et al., 1987; Bond et al., 1986; Wong, 1987). The study by Rinsky et al. (1987) has been reevaluated several times (Wong, 1995; Crump, 1994; Paxton et al., 1994). There is strong evidence of increased risk for AML at high levels of exposure; however, only limited information has been available about dose effects near the range of exposures currently common in China and the United States. More recently, studies of petroleum workers have begun to evaluate risks at levels generally <1 ppm (see A. R. Schnatter, this issue).

Before our collaborative study, the Chinese Academy of Preventive Medicine (CAPM) had completed an occupational survey identifying more than 500,000 benzene-exposed workers in China (Yin et al., 1987a). As reported in 1987 and 1989 (Yin et al., 1987b, 1989) the investigators from the CAPM also carried out a follow-up survey of 28,460 benzene-exposed and 28,257 unexposed workers during 1972–1981, finding an increased risk of mortality due to leukemia in the exposed group. However, mortality from all causes combined was also substantially greater in the exposed than in the unexposed, suggesting possible differentials in the completeness of follow-up between the two groups. Further, exposure-response relationships were not quantified in the CAPM study.

Beginning in 1987, scientists from the CAPM and the U.S. National Cancer Institute (NCI) undertook a collaborative CAPM–NCI study of benzene exposure and cancer risk in China (Hayes et al., 1996; Yiu et al., 1996). The CAPM–NCI study was designed independently of the earlier CAPM study, and was characterized by a substantially increased population sample size, rigorous methods of subject ascertainment, exposure assessment, subject follow-up, case ascertainment, and case verification of diagnosis of lymphohematopoietic malignancies by expert hematopathologists. Among the reasons for carrying out this study in China were the large number of benzene-exposed workers, with a broad range of exposure levels, the varied industrial settings of the exposures, the relative stability of jobs held in the workforce, the availability of factory records containing exposure information, the availability of monthly salary records for ascertainment of individual job histories, and the cooperation of local occupational health staff and factory management, through all phases of the study.

METHODS

Cohort Identification

The cohort of benzene-exposed workers was comprised of men and women employed between 1972 and 1987 in 1427 benzene-exposed work units (departments) in 672 factories in 12 cities in China. Various industries and occupations using benzene were studied, including painting, printing, and manufacture of footwear, paint, and other chemicals. An

unexposed comparison group was assembled from workers employed between 1972 and 1987 in work units where benzene was not used in 69 of these factories and in 40 additional factories (Dosemeci et al., 1994; Yin et al., 1994). Subjects were identified from salary records and other factory written administrative records. We abstracted demographic data, including name, birth date, sex, and occupational data, including the dates of employment, by work unit and job title, for all jobs held by subjects in the study factories.

Exposure Assessment

For benzene exposure estimation, we developed a standardized job-title dictionary comprised of 60 benzene exposure-specific job titles in 11 major activity groups. Exposure was estimated for each benzene-exposed job, during 5-yr calendar periods, by a factory exposure assessment team consisting of industrial hygienists, safety officers, and other employees, following a predetermined exposure assignment algorithm (Yin et al., 1994). Using, but not relying solely on, available air measurements of benzene (n = 8477) and abstracted data on benzene use and working conditions, an estimated benzene exposure level was assigned to one of 6 concentration ranges (<1 ppm; 1–5 ppm; 6–10 ppm; 11–25 ppm; 26–50 ppm; and >50 ppm) for each job in 7 calendar periods (1949–1959, 1960–1964, 1965–1969, 1970–1974, 1975–1979, 1980–1984, and 1985+). Following exposure assignment, data abstraction forms were edited and reviewed to evaluate consistency between the estimated level and the sources of exposure information. If additional information was needed, this was sought in order to resolve discrepancies between assigned benzene exposure estimates and the abstracted exposure information.

Subject Follow-Up

Subjects were followed up for history of benzene toxicity, selected lymphohematopoietic malignancies and other hematologic disorders and for vital status to December 31, 1987, through factory salary and personnel records at study factories and subsequent places of employment, or, as needed, by contacting next of kin, work colleagues, treating physicians, or others. For deceased subjects, cause of death was obtained from employer medical records, other written factory records, or death certificates. Only after extensive search had failed to locate written records listing cause of death were treating physicians or next of kin contacted.

Case Verification

For cases newly diagnosed with lymphohematopoietic malignancies and other hematologic disorders during the period of follow-up, pertinent histopathologic material, pathology reports, and medical records were requested. For pathology review, clinical, laboratory, and pathologic data were abstracted onto standardized forms by U.S. and Chinese physician

investigators. All available histopathologic and bone-marrow aspirate slides and peripheral blood smears were reviewed systematically, by expert hematopathologists affiliated with the NCI, the Mayo Clinic, and the Peking Union Hospital, Beijing, using structured abstract forms to objectively characterize specific type and features of each potential case of a lymphohematopoietic disorder. Diagnoses were assigned without knowledge of the patient's benzene exposure status. Published criteria were used to categorize leukemia by cell type and, if possible, by the French–American–British (FAB) Classification subtype. Lymphoma cases were characterized by morphologic features, if feasible; lack of detailed morphology or immunohistochemical staining limited further characterization of most cases. This review also revealed cases of myelodysplastic syndromes (MDS) (Travis et al., 1994; Linet et al., 1996). For selected analyses, ANLL and MDS were combined as one disease category because of possible commonalities in the natural history of these conditions, and failure in the past to consistently classify MDS as entities distinct from ANLL.

Statistical Analysis

For the statistical analysis, person-years were accumulated for the benzene-exposed workers from January 1, 1972, or, if hired later, from the first date of employment in a benzene-exposed job. For the unexposed comparison group, person-years were accumulated from January 1, 1972, or, if hired later, from the first date of employment. Analyses for mortality due to all causes and for incidence of lymphohematopoietic malignancies and other hematologic disorders were made by internal comparison of disease rates in the benzene-exposed group to the rates in the unexposed group, by Poisson regression analysis, yielding rate ratios (RR) for exposed versus unexposed workers, with statistical adjustment for age and, where appropriate, for sex. Statistical variability in the risk estimates was expressed as the 95% confidence interval on the RR.

Dose-response was assessed with respect to duration (<5, 5–9, 10+ yr), average (<10, 10–24, 25+ ppm), and cumulative exposure (<40, 40–100, 100+ ppm-yr) to benzene. For dose-response analyses, each measure of benzene exposure for each individual was allowed to change with time; person-years and disease events were assigned to benzene exposure levels with a 1.5-yr lag (i.e., according to the estimated benzene exposure level for the time period 1.5 yr prior to the time at which disease risk was being estimated). In order to further evaluate the temporal component of disease development, we partitioned cumulative exposure at a given time into recent (1.5 yr to 10 yr earlier) and distant (10 yr or more earlier) exposure. Because a substantial number of workers were exposed to a relatively stable average amount of benzene, we also developed a measure designated as constant exposure, where follow-up was censored beginning 1.5 yr after the individual's exposure level changed (<10 ppm, 10–24 ppm, 25+ ppm) for the first time.

Study Group

The study group consisted of 74,828 benzene-exposed and 35,805 unexposed workers. On average, benzene-exposed subjects were followed for 10.5 yr, while unexposed subjects were followed for 11.7 yr. Women contributed 47% of the person-years in the benzene-exposed study group and 40% in the unexposed group. Overall, the study groups were young, with about 60% of the total person-years at risk being contributed by subjects less than 30 yr of age at study entry. About 2 percent of study subjects died during the follow-up period (1369 benzene-exposed and 598 unexposed). Only 147 exposed and 90 unexposed workers were lost to follow-up.

RESULTS

Eighty-one incident cases of lymphohematopoietic malignancies (n = 63) and selected other hematologic disorders (n = 18) (agranulocytosis, aplastic anemia, and myelodysplastic syndromes [MDS]) were found among 74,828 benzene-exposed workers, and 13 lymphohematopoietic malignancies were identified among the unexposed comparison group of 35,805 workers (Yin et al., 1996). Risk was significantly elevated for all lymphohematopoietic malignancies combined (RR = 2.6), total malignant lymphomas (RR = 3.5), and total leukemias (RR = 2.6). Among the leukemia subtypes, only AML was significantly elevated (RR = 3.1), although nonsignificant excesses were also noted for chronic myeloid leukemia (CML) (RR = 2.6) and lymphocytic leukemia (RR = 2.8), the latter attributable to 5 cases of acute lymphocytic leukemia. Significant excess risks were also found for aplastic anemia (based on 9 cases in exposed workers and none in the unexposed) and MDS (based on 7 cases in the exposed workers and none in the unexposed). The relative risk for the rubric of AML/MDS was RR = 4.1. The relative risk for all lymphohematopoietic malignancies and other hematologic disorders combined was 3.4 and for non-Hodgkin's lymphoma (NHL) RR = 3.0. No cases of Hodgkin's disease were identified. Risks of total and specific types of lymphohematopoietic malignancies and other types of cancers were similar for men and women (Li et al., 1994). Risk for ANLL/MDS was substantially increased (RR = 70.6), however, among workers with a prior history of benzene poisoning (Rothman et al., 1997).

Risk for ANLL/MDS was significantly elevated among workers hired before 1972 (the beginning of the cancer risk assessment period) (RR = 4.0) and later (RR = 5.1). Although occupation-specific results were limited by small numbers, risks for ANLL/MDS were elevated among coatings workers (RR = 4.2), rubber workers (RR = 6.1), chemical workers (RR = 4.5), and among those with other or mixed occupations (RR = 4.4) (Hayes et al., 1997). Risk for NHL was also elevated among several occupational groups, but only chemical workers showed a statistically significant excess (RR = 7.8).

ANLL and ANLL/MDS both showed patterns of increasing risk with increasing average exposure to benzene, with more consistent exposure-response patterns for ANLL/MDS than for ANLL alone (Hayes et al., 1997). The link of ANLL/MDS with average exposure was strongest when restricted to subjects with constant levels of exposure: Risks rose from 3.2 for those with constant low-level exposures (<10 ppm) to 7.1 for those with constant high-level exposures (25+ ppm). Risk for ANLL/MDS increased with increasing cumulative exposure to benzene, but the highest risks were not seen in the highest exposure level (cumulative ppm-yr: 40–99, RR = 6.0; cumulative ppm-yr: 100+, RR = 4.4). Although there was some evidence of increased risk for leukemias other than ANLL among benzene-exposed workers, clear patterns of increasing risk with increasing exposure were not observed, and small numbers of specific types of leukemia other than ANLL precluded more detailed analyses.

Risk of ANLL/MDS was sixfold and significantly increased among those who had only recent benzene exposure (14 exposed cases). Risk of ANLL/MDS was also strongly associated with increasing amounts of recent (p for trend = .003) but not distant benzene exposure (p for trend = .51). NHL was strongly linked with distant exposure to benzene (p for trend = 0.005, 13 exposed cases), but the association with exposure in the most recent 10 yr was weak (p for trend = .15, 16 exposed cases).

There were 412 documented as having benzene poisoning among 62,234 exposed subjects in 11 of the study cities. (Data on benzene poisoning from the 12th city were difficult to interpret because of some differences in the criteria used to establish the diagnosis of this condition.) Risks for benzene poisoning increased with increasing intensity of exposure at one and a half years prior to diagnosis of benzene poisoning (<5 ppm, RR = 1 [referent]; 5–19 ppm, RR = 2.2 [95% CI = 1.7–2.9]; 20–39 ppm, RR = 4.7 [95% CI = 3.4–6.5]; and 40+ ppm, RR = 7.2 [95% CI = 5.3–9.8]). Relative risks of benzene poisoning by cumulative exposure were 1.7 (95% CI = 1.3–2.3), 2.0 (95% CI = 1.5–2.6), and 2.4 (95% CI = 1.8–3.2) for cumulative exposure of 40–99 ppm-yr, 100–399 ppm-yr, and 400 ppm-yr and more, respectively, compared to subjects who had less than 40 ppm-yr cumulative exposure to benzene (Dosemeci et al., 1996).

Translational Studies

Detailed methods and further results for these studies are presented elsewhere in this issue (this issue, M. T. Smith & N. Rothman). Briefly, selected biomarkers were assessed among workers heavily exposed to benzene (n = 44; median benzene exposure: 31 ppm as an 8-h time-weight average [TWA]), among workers with a history of benzene poisoning (n = 50; benzene poisoning based upon routine hematologic exams), and among unexposed controls, in Shanghai, China.

Workers currently exposed to benzene had lower counts for white blood cells, lymphocytes, platelets, and red blood cells, and a lower hema-

tocrit (Rothman et al., 1996a); however, lymphocyte count was the most sensitive indicator of benzene-induced hematotoxicity. Benzene air levels correlated with urinary levels of phenol, muconic acid, hydroquinone, and catechol; however, among those with the highest exposure to benzene, hydroquinone and muconic acid levels tended to plateau as a proportion of benzene metabolites.

Workers with a history of benzene poisoning were more likely than comparison controls to be rapid excretors of chlorzoxazone, an indicator of CYP2E1 activity, and to have two copies of the NQ01 609C-T mutation (combined odds ratio (OR) = 7.6) (Rothman et al., 1997). CYP2E1 and NQ01 enzymes are involved, respectively, in activation and detoxification of benzene and its metabolites, suggesting that genetic determinants of benzene metabolism may influence risk of benzene poisoning, which itself is a risk factor in our cohort study for ANLL/MDS (RR = 70.6).

DISCUSSION

The CAPM–NCI study identified 30 ANLL/MDS, 9 aplastic anemias, and 19 non-AML leukemias among 74,828 benzene-exposed workers. Risks for AML and aplastic anemia were elevated, as previously described (IARC, 1982). In a new finding, we also showed excess risks for MDS in benzene-exposed workers.

Although early case series of benzene-exposed workers noted abnormalities in bone marrow and peripheral blood consistent with MDS in some pancytopenic patients prior to the development of acute leukemia (Van den Berghe et al., 1979; Aksoy & Erdem, 1978; Goguel et al., 1967), the recognition of myelodysplastic syndromes is relatively recent and has not routinely been considered in evaluations of risk associated with benzene exposure. Cases of MDS have reported prior exposure to solvents (Vineis et al., 1990) and to benzene (Ciccone et al., 1993), and a case-control study in Great Britain (Mehlman, 1987) showed an association of MDS with a history of exposure to gasoline and diesel fumes or liquids. It is noteworthy that a myelodysplastic phase precedes overt leukemia in a large proportion of AML related to treatment with alkylating agents (Pedersen-Bjergaard & Philip, 1987; Michels et al., 1985), suggesting that a similar pathogenesis could occur with benzene.

Our study showed that benzene may cause lymphohematopoietic malignancies and related disorders at lower exposure levels than previously described. Limited to workers who did not change jobs from one exposure level to another, the risk for ANLL/MDS at <10 ppm was RR = 3.2 (10 cases, 95% CI 1.0–10.3), at 10–24 ppm was RR = 5.1 (4 cases, 95% CI 1.3–20.6), and at 25+ ppm was RR = 7.1 (8 cases, 95% CI 2.1–23.7). In the Pliofilm cohort of 1165 rubber hydrochloride manufacturing workers in the United States, 6 cases of AML were identified (Wong, 1995). In this cohort, a highly significant 50-fold excess of AML was found at cumulative expo-

sures of >200 ppm-yr (5 cases, 0.1 expected). Although the Pliofilm cohort established risks at high levels of exposure (>200 ppm-yr), the study provides little, if any, direct information about risks at <200 ppm-yr. No increases in risk were found for those exposed to <40 ppm-yr (1 case, 0.84 expected, SMR = 1.19, 95% CI 0.03–6.63) or those exposed to 40–200 ppm-yr of benzene (0 cases, 0.25 expected, SMR = 0, 95% CI 0–14.75), but the 95% confidence intervals were extremely broad, essentially encompassing either a strongly protective effect or a substantially elevated risk.

While the precise shape of the benzene exposure-response curve can only be estimated with caution from either of these studies, only our larger study had sufficient power to provide quantitative estimates over a broad range of exposures. In assessing the findings from the China study, certain design aspects should be recognized.

Choice of Comparison Population

We compared the disease rates of benzene-exposed workers to the rates for nonexposed workers in the same plants or in similar occupational settings. As earlier described by Wong (1987), this is the most appropriate basis for comparison in occupational studies. Supporting the suitability of the unexposed study group for disease comparisons, in the CAPM–NCI study the benzene-exposed and comparison groups had strikingly similar overall patterns of mortality, with statistically significant increases found only for occupational injuries/poisoning, lymphohematopoietic malignancies, and lung cancer (Hayes et al., 1996). The unexpected excess for lung cancer is currently under investigation.

Because disease rates in an industrial comparison group are subject to statistical variation (in contrast to statistically stable national rates), there is, however, a trade-off of less statistical power for the gain in validity. Clearly, a larger population size or longer periods of follow-up of this cohort would lead to reduced statistical variation and more precise estimates of risk. This statistical uncertainty is, however, accounted for in our study by the reported p value and confidence limit ranges. Small SMR studies are also subject to substantial statistical variation, as described earlier for the analysis by Wong (1995).

Benzene Exposure Estimation

The exposure estimation procedure used available benzene exposure measurements and other information on the industrial process, including types of materials used, percent of benzene in benzene-containing materials, frequency of exposure, changes in engineering controls, and other control measures (Dosemeci et al., 1994). The purpose of this procedure was to estimate average workday exposures. The available historical benzene exposure measurements, which were short-term "grab" samples, served as one component of the data used for exposure assessment. How-

ever, these sample measurements were not collected for epidemiologic purposes and often do not represent usual exposure conditions. Thus, historical exposure levels estimated for workers in our study can differ from the benzene exposure measurements reported in a given work unit.

Exposure estimates were developed for each job title, work unit, factory, and time period. To summarize this procedure, we presented averages for these estimates across all study factories for major industry (Table III, Dosemeci et al., 1994) and occupation groups (Table IV, Dosemeci et al., 1994); however, the specific job/work unit/factory estimates were used for subjects in the epidemiologic analysis. Thus, for example, a spray painter working in a particular factory and work unit in Shanghai where exposure measurements averaged about 100 ppm for the period 1965–1969 was assigned to the highest benzene exposure category of >50 ppm (Figure 2, Dosemeci et al., 1994), while the average exposure for all spray painters in the study during that period was only about 20 ppm (Table IV, Dosemeci et al., 1994).

It should also be noted that the cross-sectional translational studies of benzene-exposed workers that we carried out in conjunction with the cohort study involved a small group of selected factories, which were expressly chosen to represent a wide range of benzene exposures. The factories were all located in one city and are not representative of the distribution of exposures among the total study cohort in these occupational categories (Rothman et al., 1996b).

The validity of the exposure assessment approach was supported by the correlation of estimated benzene levels with the occurrence of benzene poisoning (Dosemeci et al., 1996). The strong association between our exposure estimates and hematological abnormalities long documented in relation to benzene exposure strongly suggests that the ranking of individuals with respect to exposure was successful. Beyond mere ranking, the result also suggests that the actual ranges of exposure were estimated with a fair degree of accuracy, because successful ranking for the total study could not have been achieved by the staff in the 12 study cities without substantial concordance on what actual levels of exposure were. Clearly, over time there was heterogeneity in the quality of the data used for exposure assessment; however, systematic under- or overestimation is unlikely to have occurred. As such, random error in the exposure assessment would lead under realistic misclassification scenarios to attenuation of the dose-response curves, resulting in underestimated risks for a given level of exposure (Rothman, 1986).

Confounding and Effect Modification

Life-style factors could confound an occupational association with disease, if the factor causes the disease and is strongly associated with the occupational exposure under study. For ANLL there are no obvious exposures that may be life-style candidates, except possibly cigarette use, which

has been associated in some studies with an approximately 50% increase in leukemia risk (Linet & Cartwright, 1996). Axelson and Steenland demonstrated, however, that correlations between cigarette use and occupational exposure need to be quite strong to result in even modest confounding for lung cancer (Axelson & Steenland, 1988). For a disease much more weakly associated with smoking, such as leukemia, the confounding effects would be even less substantial. As Siemiatycki et al. (1988) have demonstrated in another setting, it is unlikely that tobacco use correlates sufficiently strongly with exposure in our study population, such that it would account for the dose-related effects attributed to benzene. The exposed and unexposed study groups in our study derived from similar occupational backgrounds, and it is unlikely that they differ substantially with respect to such life-style factors.

As in most industrial settings, the workers in this investigation were likely exposed to a number of chemicals other than benzene; in principle, the observed excesses for ANLL could be due to these exposures. However, no other specific industrial exposure, except ionizing radiation, has been consistently linked to ANLL (Linet & Cartwright, 1996). As radiation is not a factor in our study, unmeasured industrial confounders for the observed association with benzene remain entirely speculative. In addition, the subjects in this study were employed in a variety of industries and occupations, and excesses of ANLL/MDS were not restricted to any particular subset of jobs (Hayes et al., 1997). This strongly suggests that the observed increased risks for these conditions are due to the common exposure to benzene. We noted, however, that an excess of NHL was found in our study, which could potentially be attributed to other exposures, as the excesses were significant only in the subset of benzene-exposed chemical workers.

Several factors may modify the uptake, distribution, biotransformation, or excretion of benzene, including physical activity (work load), body composition, age, sex, genetic polymorphisms of biotransformation, ethnicity, diet, smoking, drug treatment, and coexposure to ethanol and other solvents, such as toluene and xylene (Lof & Johanson, 1998). It is important, however, to distinguish between potential effect modifiers and those for which there is solid scientific support. For example, toluene acts antagonistically on benzene metabolism and toxicity at very high doses, suggesting potential effect modification of benzene-associated cancer risk; however, no effect has been seen of toluene on the macromolecular binding of benzene in liver and bone marrow at human-relevant doses (Carver et al., 1999). Only recently are translational studies beginning to elucidate some of the complexities in benzene carcinogenesis in humans (see M. T. Smith & N. Rothman, this issue; and Rothman et al., 1996b, 1997), and the impact of these factors on cancer risk in humans remains to be evaluated.

We provided evidence that ANLL/MDS was most closely linked to recent benzene exposure (<10 yr) (Hayes et al., 1997). If both level and tem-

poral pattern of exposure determine risk, then it may be difficult to assess the relevant exposures for subjects who change exposure levels; in this case, simple cumulative exposure scores may misclassify subjects. Consistent with this, we found the strongest associations with risk for ANLL/MDS among the subset of workers who did not change category of benzene exposure during their employment in the study plants.

Case Validity

In contrast to earlier benzene cohort investigations, which relied primarily on death certificate studies to validate disease outcomes, in the CAPM–NCI study we assessed incidence and mortality due to lymphohematopoietic malignancies and related disorders. To minimize disease misclassification, we also carried out a detailed clinical and pathologic review, with suspected lymphohematopoietic disorders reviewed carefully by expert hematopathologists in the United States and China (Linet et al., 1996; Travis et al., 1994).

Disease Surveillance

Because benzene-exposed workers are known to be at excess risk for leukemia, it is possible that cases were identified earlier in the disease process in the exposed group than in the unexposed group, due to more thorough disease surveillance. This could not have substantially affected our results, because ANLL is lethal and most of the cases died during the study period. Survival from ANLL was similar for exposed and unexposed workers, and risk estimates were similar when restricted to exposed and unexposed deceased cases (Yin et al., 1996). Loss to follow-up was low (0.2%), so missed cases of hematopoietic malignancies would be unlikely to influence the results.

Benzene and Other Hematopoietic Malignancies

Aside from the associations with ANLL/MDS and aplastic anemia, the study provided evidence that other hematopoietic malignancies may be linked to benzene exposure. These results, however, need further study.

SUMMARY

While this study is larger than previous investigations and includes workers with a wide range of exposures to benzene, the estimates of risk, as measured by statistical confidence intervals, are still fairly broad, and would benefit from the larger numbers that could be provided by continued follow-up of this population. Nevertheless, the study confirms earlier findings of increased risk for ANLL and aplastic anemia among benzene-exposed workers, provides the first substantial evidence that MDS is linked to benzene exposure, and provides evidence that benzene increases risk for ANLL/MDS at lower levels of exposure than had previously been

demonstrated. Currently we are evaluating the potential for extending the follow-up of workers included in this study. A new study would include expanded data collection for cases of hematopoietic malignancy and related disorders and for an appropriate control series.

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